LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bulgaplin
(pregabalin)

SE/H/2364/01-07/DC

This module reflects the scientific discussion for the approval of Bulgaplin. The procedure was finalised on 2024-01-17. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Bulgaplin, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 225 mg, 300 mg, capsule, hard.

The active substance is pregabalin. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Bulgaplin, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 225 mg, 300 mg, capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS), and with EE, LT, LV and PL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Lyrica, 25 mg, capsule, hard, authorised in EU since 2004, with Upjohn EESV as marketing authorisation holder.

The reference product used in the bioequivalence study is Lyrica, 300 mg, capsule, hard from Greece with Upjohn EESV as marketing authorisation holder.

Potential similarity with orphan medicinal products

N/A

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of pregabalin are well known. As pregabalin is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Bulgaplin is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Bulgaplin from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Bulgaplin with the reference product Lyrica.

Pharmacokinetic properties of the active substance
Absorption: Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose.

The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25-30% and a delay in t_{max} to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption. There are no restrictions with respect to food in the SmPC of the originator.

Linearity: Pregabalin pharmacokinetics are linear over the recommended daily dose range.

Elimination: Pregabalin mean elimination half-life is 6.3 hours.

Study 100-13
Methods
This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Pregabalin, 300 mg, capsules with Lyrica, 300 mg, capsules under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of pregabalin were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2013-10-08 and 2013-10-18.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for pregabalin, n=20.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**72018 ± 10262**	**8941 ± 1337**	**1.50 (0.75-3.02)**
Reference	**72165 ± 10735**	**8765 ± 1856**	**1.50 (0.75-4.00)**
***Ratio (90% CI)**	**99.9 (97.26-102.65)**	**103.3 (95.35-111.92)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

A biowaiver was sought for the additional strengths of 25, 50, 75, 100, 150 and 225 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr).

Absence of studies with the additional strengths of 25, 50, 75, 100, 150 and 225 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of pregabalin is linear over the recommended daily dose range.

Based on the submitted bioequivalence study, Bulgaplin is considered bioequivalent with Lyrica.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bulgaplin.

Part II Safety specification

The MAH has submitted the version 5 RMP dated 2023-08-16 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• Dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury • Discontinuation events • Drug interactions (lorazepam, ethanol, and CNS depressants) • Euphoria • Congestive heart failure • Vision-related effects • Abuse and drug dependence
Important potential risks	• Suicidality • Off-label use in paediatric patients
Missing information	None

Assessor's comment: Having considered the data in the safety specification the assessor agrees that the safety concerns listed by the MAH are appropriate.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 5 signed 2023-08-16 for Bulgaplin is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet for Bulgaplin has been performed on the basis of a bridging report making reference to Burana DE/H/5281/01/DC regarding layout, and Pregabalin Jubilant SE/H/1807/01-08/DC regarding content.
The bridging report for Bulgaplin submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Bulgaplin is found adequate. There are no objections to approval of Bulgaplin from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk ratio is considered positive, and Bulgaplin, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 225 mg, 300 mg, capsule, hard, is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Bulgaplin, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 225 mg, 300 mg, capsule, hard, was positively finalised on 2024-01-17.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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